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Health Effects of Uranium Exposure

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TECHNICAL REPORT
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Abstract

This manuscript summarises the risks associated with uranium exposure. Experimental data is available from genetics, tissue culture, and animal and human models. Studies include solubility of different uranium compounds, kinetic properties inside the body, and short- and long-term health effects both from acute and chronic exposures. The potential for uranium entry into the body is highly dependent upon its chemical and physical properties. Inhalation and dermal contact afford the most rapid route of entry, while gastrointestinal absorption is often minimal. The kidneys are efficient at clearing uranium dissolved in the blood, usually within days. Insoluble forms of uranium such as imbedded shrapnel can remain in the body for many years, resulting in persistent elevated levels of uranium in urine. The most important potential for uranium toxicity lies with its chemical properties – not its radiological properties. The most probable health outcomes for uranium toxicity are kidney disease and cancer. Limited data suggests that cumulative pulmonary exposure up to 25 cGy probably does not increase the risk of lung cancer. Nevertheless, there are many gaps in the understanding of the toxicological profile of uranium. Filling these gaps requires monitoring exposed individuals for long periods of time due to the range of latency periods between exposure and health outcome diagnosis.

Résumé

Ce document résume les risques associés à l'exposition à l'uranium. Les données expérimentales proviennent d'études génétiques, d'essais avec la culture de tissus, et de modèles humains et d'animaux. Les études incluent la solubilité des différents composés d'uranium, leurs propriétés cinétiques dans le corps, et les effets à court terme et à long terme des expositions aigües et chroniques. Le potentiel de pénétration de l'uranium dans le corps dépend grandement de ses propriétés chimiques et physiques. La pénétration la plus rapide se fait par l'inhalation et par la peau, tandis que l'absorption gastrointestinale est souvent minime. L'uranium dissous dans le sang est éliminé en l'espace de quelques jours par les reins. Les formes insolubles de l'uranium, tel que le shrapnel, peuvent demeurer dans le corps pendant plusieurs années, ce qui peut engendrer des niveaux élevés d'uranium dans l'urine. La toxicité la plus importante de l'uranium est causée par ses propriétés chimiques – et non pas à ses propriétés radiologiques. Les effets les plus probables sur la santé dûs à la toxicité de l'uranium touchent surtout les maladies rénales et le cancer. Des données limités suggèrent qu'une exposition pulmonaire cummulative jusqu' à 25 cGy n'augmente probablement pas le risque de cancer du poumon. Toutefois, la compréhension du profile toxicologique de l'uranium comporte encore plusieurs lacunes. Pour remplir ces lacunes, il faudra faire un suivi continu chez les individus exposés en raison de l'étendue des périodes de latence entre l'exposition et le diagnostic de la maladie.

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Executive summary

To better understand the potential health risk associated with uranium exposure, Director General Nuclear Safety tasked Radiation Biology at Defence Research Establishment Ottawa with producing a literature review of the current state of knowledge regarding uranium exposure and toxicity. The data in this document summarises the known routes of uranium entry into the body, mechanisms of toxicity, clinically relevant manifestations of pathology for organs that are the principal sites of uranium accumulation, and known final health outcomes.

Following exposure, the kinetics of uranium distribution are primarily dependent on the solubility of its chemical form and the site of entry into the body, where the lung has been identified as offering the most rapid route of incorporation into the blood. Following dissolution into the blood, the principal sites of accumulation are the kidneys, bones and liver.

Many authors have acknowledged that the importance of uranium as a chemical toxin greatly outweighs its importance as a radiological toxin, as repeatedly demonstrated by animal models. In the case of kidney disease, this study concludes that uranium probably does not induce clinically significant renal dysfunction, except in cases of massive overexposure (ingestion of tens of grams of highly soluble uranium). Regarding uranium ingestion, gastric absorption was found to be minimal, and there have been no reported negative health effects. Although some *in vitro* and/or *in vivo* animal models have demonstrated dermal, neurological, mutagenic, skeletal and reproductive effects at very high uranium exposures, similar effects in humans have not been reported.

Regarding cancer, available data from uranium workers indicates that uranium exposure probably does not increase the probability of developing cancer. The most likely cancer forms are believed to be: lung, bone, and lymphatic cancer. With respect to pulmonary exposure – which is the most common scenario – cumulative exposure up to 25 cGy probably does not increase the risk of lung cancer. Currently, there is insufficient data to suggest or refute a relationship between uranium exposure and bone or lymphatic cancer. The most important potential for answering these questions lies with continued follow-up studies of the cohorts of civilian uranium workers because of the range of latency periods between exposure and disease diagnosis.

Stodilka RZ. 2001. Health Effects of Uranium Exposure. TR 2001-044. Defence Research Establishment Ottawa.

Sommaire

Ce document est un sommaire de l'état actuel des connaissances des effets de l'exposition à l'uranium sur la santé. Les données résument les routes connues de pénétration de l'uranium dans le corps, les mécanismes de toxicité, les manifestions pathologiques pertinentes dans les organes qui sont les principaux sites d'accumulation d'uranium, et les effets définitifs sur la santé.

Après l'exposition à l'uranium, la cinétique de sa distribution dépend principalement de la solubilité de sa forme chimique et du site de pénétration dans le corps – où le poumon a été identifié comme la route d'incorporation la plus rapide dans le sang. Les principaux sites d'accumulation sont les os, les reins et le foie.

Beaucoup d'auteurs ont reconnu que l'importance de l'uranium comme toxine chimique est considérablement supérieure à son importance comme toxine radiologique - comme ce fut démontré à plusieurs reprises sur les modèles d'animaux. Dans le cas des maladies de reins, cette étude conclut que l'uranium n'induit probablement pas d'anomalie rénale significative, sauf dans des cas de surexposition massive (ingestion de dizaines de grammes d'uranium fortement solvable). L'absorption gastrique après l'ingestion d'uranium s'est avérée minimale, et aucun effet négatif sur la santé n'a été décelé. Bien que quelques modèles d'animaux *in vitro* et *in vivo* aient démontré des effets cutanés, neurologiques, mutagéniques, squelettiques et reproducteurs à des concentrations d'uranium très élevées, des effets semblables chez l'homme n'ont pas été notés.

Les données obtenues chez les ouvriers civils travaillant avec l'uranium indiquent que l'exposition à l'uranium n'augmente pas la probabilité de développer un cancer. Les formes de cancer les plus probables sont le cancer du poumon, des os et du système lymphatique. En ce qui concerne l'exposition pulmonaire - qui est le scénario le plus commun – une exposition cummulative jusqu' à 25 cGy n'augmente probablement pas le risque de cancer du poumon. Actuellement, il n'y a pas suffisamment de données pour suggérer ou réfuter un lien entre l'exposition à l'uranium et le cancer des os ou du système lymphatique. Le meilleur moyen de répondre à ces questions est de faire un suivi continu chez les ouvriers civils travaillant avec l'uranium en raison de l'étendue des périodes de latence entre l'exposition et le diagnostic de la maladie.

Stodilka, RZ. 2001. Effets de l'exposition à l'uranium sur la santé. TR 2001-044. Centre de recherce pour la défense Ottawa.

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1. INTRODUCTION

This purpose of this document is to provide the Department of National Defence with a general perspective of the toxicology of uranium. It presents information regarding modes of entry of uranium into the body, biokinetics, acute and chronic effects on critical organs, and modes of excretion. Information was drawn from a broad spectrum of literature: from basic toxicology using animal models, to epidemiological investigations of large cohorts of uranium miners.

It is widely believed that the health effects of uranium exposure are a result of chemical – rather than radiological – toxicity, and this is reflected by nearly all toxicological studies. Although some early reports have linked occupational exposure of uranium to lung carcinogenesis, it is now believed that this is due to the inhalation of radon and its progeny, and the toxicity of uranium *proper* is not involved [US NRC 1988, Vahakangas *et al* 1992, IOM 2000]. Further, although the skeleton is widely acknowledged to be a principle reservoir for uranium storage [Kathren *et al* 1989], no excess bone cancer has been reported in exposed cohorts. In the case of Gulf War Veterans, radiation dose from internalised depleted uranium is thought to be small. In a recent study of the health effects of depleted uranium on nine exposed Gulf War Veterans, McDiarmid *et al* [2000] found committed effective dose equivalent values to fall between 0.12 mSv and 1.1 mSv per year for the Veterans – below the estimated background level of exposure of 3.65 mSv. Of this group, one veteran was found to have a committed effective dose equivalent higher than the NRC annual exposure allowance to the public (1 mSv). Given these low exposure levels, the authors suggest that uranium's chemical toxicity, therefore, presents the principal concern to Gulf War Veterans, with particular focus on the nephrotoxic effects that uranium shares with other heavy metals, and its acute toxic effects on the respiratory system.

Chemical toxicity is identical for all uranium isotopes because it only depends upon chemical properties; thus chemical toxicity for a given mass of enriched, natural or depleted uranium is identical. The potential for toxicity is dependent upon a number of factors including peak and average tissue concentration.

This study focuses on organs and organ systems that are the principle targets for uranium deposition following intoxication. Special attention is drawn to lung contamination and toxicity because it has been identified as an important route of entry. Additional emphasis was placed on investigating the potential for neurotoxicity since this may be of interest to Gulf War Veterans. Finally, the potential for uranium-induced kidney disorders was analysed because many authors suspect the kidney to be the sentinel organ for toxicity.

2. DISTRIBUTION OF URANIUM IN THE BODY

Given an exposure, the rate of uranium entry into the body depends upon chemical form and solubility, physical form, and mode of entry into the body. Generally, more soluble forms with greater [surface area : mass] ratios present the greater risk. Equivalently, areas of the body encouraging solution or presenting large interfacial surface areas present the most rapid routes of entry. Soluble forms present a risk for general systemic toxicity, while insoluble forms present more localised risk since they are more likely to be retained at the site of entry [Leach *et al* 1970].

Regardless of the site of entry, once inside the body, distribution is primarily through blood. Uranium has been shown to complex with carbonates, proteins, minerals, and phospholipids [Dounce and Flagg 1949, Neumann and Tishkoff 1953, Blake *et al* 1956, Cooke and Holt 1974, Schullery and Miller 1977], and small quantities can distribute through lymph [Leach *et al* 1970, 1973]. Chevari and Likhner [1968] indicate approximately 47% of blood uranium complexes with bicarbonates in plasma, 32% binds to plasma proteins, and 20% binds to red blood cells. However, most studies show no measurable effect of uranium on haematological parameters. For example, Gilman *et al* [1998] studied uranyl nitrate toxicity over 91 days using a rabbit model. Rabbits were exposed to uranyl nitrate concentrations between 0.96 and 600 mg / L through drinking water (typical uranium levels in Canadian drinking water are less than 1 mg / L [Limson Zamora *et al* 1998]). The authors did not observe any dose-dependent effect on haematological parameters. Similarly, in a recent study of Gulf War Veterans, uranium was reported to not affect haematological parameters (hematocrit, hemoglobin, platelet, neutrophil, basophil, eosinophil, and monocyte frequencies) [McDiarmid *et al* 2000].

Uranium entering the circulatory system in acute doses is rapidly cleared into tissues and excreted mostly in urine within days. For example, in humans intravenously injected with uranium, the amount of uranium remaining in the blood after 5 minutes, 5, 24, and 100 hours was found to be 25%, 5%, 1%, and less than 0.5% [ICRP 1995]. Intravenous injection models are used to mimic single exposures [Morrow *et al* 1982]. Regarding excretion from the body, ICRP [1995] reports that in humans intravenously injected with uranium, approximately 65% was excreted in the urine within 24 hours, and an additional 10% excreted over the following 5 days.

Animal models [Ballou *et al* 1986, Diamond *et al* 1989, La Touche *et al* 1987, Morrow *et al* 1982, Neumann *et al* 1948, Voegtlin and Hodge 1949, Walinder 1989] and epidemiological studies [Kathren *et al* 1989, Singh *et al* 1987] have demonstrated that the skeleton and kidney are the primary reservoirs for uranium, transferred from blood, regardless of the route of exposure. Post-mortem studies of uranium injected humans have shown that a subject dying 2.5 days following injection retains approximately 10%, 14%, and 6% of the administered dose in the skeleton, kidney and other soft-tissues, respectively [ICRP 1995]. However, small fractions of dissolved uranium in the blood will enter into most organs. Animal models have shown that

following injection, uranium is distributed to bone, kidney, spleen and liver [Morrow *et al* 1982, Neuman *et al* 1948, Walinder 1989].

Pellmar *et al* [1999a] studied uranium distribution using a rat model of intramuscularly implanted uranium pellets. The pellets were 1mm diameter and 2 mm long, and were implanted into thigh muscles. Tantalum pellets were used as controls. Tantalum is relatively biologically inert, and is widely used for surgical purposes. Three uranium levels were used: low (4 uranium pellets), medium (10 uranium pellets), and high (20 uranium pellets). The study followed uranium distribution over 18 months, and found uranium to deposit in the skeleton, kidney, liver, spleen, brain, lymph nodes, and testicles; with the kidney and skeleton being the principal reservoirs.

In other chronic exposure studies Kathren *et al* [1989], and Singh *et al* [1987] found the highest concentrations of uranium in lung, kidney, bone and liver for occupationally-exposed miners and millers. Elevated lung concentrations here were likely caused by inhalation of insoluble forms of uranium. This principle was demonstrated by Leach *et al* [1970, 1973], who exposed monkeys and dogs to dust particles of uranium dioxide, which is relatively insoluble. Five years post-exposure, the authors reported that uranium was found predominantly (about 90%) in the lungs and tracheobronchial lymph.

In summary, uranium distribution in the body depends on solubility: soluble forms will rapidly distribute throughout the body to nearly all organs, whereas insoluble forms will remain more localized at their site of entry. Uranium is transported through the blood by complexing with a variety of molecules and cells; but no negative health effects on blood have been observed. The kidney rapidly clears dissolved uranium from the blood (within days). Large solid pieces of uranium, however, can remain in the body for many months or years.

3. PULMONARY SYSTEM EXPOSURE

3.1 Solubility in the Lungs

The respiratory system is the principal route of entrance for uranium in particulate form. Deposition is primarily governed by aerodynamic properties, while the physico-chemical properties of the particles determine clearance. When inhaled particles reach the alveoli, they can either be dissolved in the alveolar environment, or undergo phagocytosis by the alveolar macrophages and ultimately be mechanically discharged into the digestive tract.

Uranium compounds can be grouped into three categories: 1) Type F (fast dissolution) compounds that dissolve rapidly (in water), such that dissolution clearance dominates the overall lung clearance rate; 2) Type M (medium dissolution) compounds with intermediate dissolution rates, such that both dissolution and mechanical clearance rates contribute to the overall rate; and 3) Type S (slow dissolution) compounds that dissolve slowly, such that the mechanical clearance rate predominates [ICRP 1994].

Table 1.Solubilities of some uranium compounds

TYPE F (FAST)	TYPE M (MEDIUM)	TYPE S (SLOW)
Uranium hexafluoride (UF_6)	Uranium tetrafluoride (UF_4)	Uranium dioxide (UO_2)
Uranium tetrachloride (UCl_4)	Uranium trioxide (UO_3)	Triuranium octoxide (U_3O_8)
Uranium fluoride (UO_2F_2)	Ammonium diuranate ($UO_3 \cdot xH_2O \cdot yNH_3$)	
Uranyl nitrate hexahydrate		
[$UO_2(NO_3)_2 \cdot 6H_2O$]		

[Eidson 1994, IOM 2000]

In addition to chemical form, other properties such as crystallinity and specific surface area (and, hence, particle size) describe the dissolution of different specimens of the same compound [Bruno *et al* 1986, Bruno 1989]. However, their roles are secondary to chemical composition as a determining factor of dissolution rate [Eidson 1994, Ansoborlo *et al* 1998].

Highly soluble inhaled uranium is rapidly absorbed into the blood [Stradling *et al* 2000b]. For highly soluble compounds, such as uranyl hexafluoride and uranyl nitrate, the overall lung clearance rate is dominated by dissolution – rather than mechanical clearance [Bailey *et al* 1985]. Uranyl nitrate has a dissolution half-time of 1-2 days *in*

vivo. However, UF_6 and UO_2F_2 are absorbed within minutes after inhalation, prompting some researchers to suggest that they be given a separate solubility category [Marrow *et al* 1982 and Ballou *et al* 1986].

As indicated in Table 1, uranium tetrafluoride, uranium trioxide, and ammonium diuranate are compounds characterized by intermediate dissolution rates. In these cases, total lung clearance is dictated by dissolution and mechanical clearance [Bailey *et al* 1985]. The clearance rates of these compounds are highly variable among species, and, arguably, can be placed in any of Fast, Medium, or Slow solubility classes [Galibin and Parfenov 1971, Stadling *et al* 1985, Andre *et al* 1989]. For example, Andre *et al* [1989] has measured clearance half times of approximately 2-7 days in rat pulmonary macrophage cultures using uranium tetrafluoride. However, as much as 38% of individual uranium tetrafluoride specimens have been reported to clear more slowly [Eidson 1994].

In vitro dissolution half times of approximately 0.1-50 days have been measured for ammonium diuranate [Morrow *et al* 1972, Henge-Napoli *et al* 1989, Edison and Mewhinney 1980, Kalkwarf 1983, Mansur and Carvalho 1988], which are reasonably consistent with findings in humans and laboratory animals, indicating that the compound could be put into either Fast or Medium classes. In the case of uranium trioxide, human and laboratory animal experiments [Morrow *et al* 1972, Eidson *et al* 1989] and *in vitro* dissolution experiments [Harris 1961] indicate dissolution half-lives of 0.3-43 days, and thus again, either Fast or Medium classes would be appropriate. For ammonium diuranate, some specimens have been noticed to include a minor fraction with half times greater than 100 days [Eidson 1994].

For compounds with characteristics corresponding to Slow dissolution (half-times of approximately 100-10,000 days, overall pulmonary clearance rates are dominated by mechanical pulmonary clearance processes [Bailey *et al* 1985]. Examples include uranium dioxide and triuranium octoxide, which, although highly variable among samples, all are best described as having slow dissolution properties [Kalkwarf 1983, Avadhanula 1985]. Price [1989] has demonstrated that some individuals demonstrate extremely long-term retention of inhaled uranium in the thorax, which confounds clearance measurements. Causes of such a long-term retention may include immeasurably slow mechanical clearance or local retention of dissolved uranium in lung tissue. This may be the result of impaired mechanical clearance mechanisms resulting from lung disease. Other causes include particulate retention in thoracic lymph nodes or retention of dissolved uranium in bone. For example, Leach *et al* [1973] have reported prolonged retention of particles translocated from lung to thoracic lymph nodes in beagles and rhesus monkeys exposed to aerosolized uranium dioxide.

The large variability in experimental measures of aerosolized solubility may result from physical characteristics of individual aerosol specimens. Mercer [1967] demonstrates that the dissolution rate of a solid is a function of its specific surface area:

$$\frac{d\left(M/M_0\right)}{dt} = -kS(t)$$

where D=dissolution rate, M/M_0 = the normalized undissolved mass; k=the dissolution rate constant ($g/m^2/day$); S=the specific surface area (m^2/g); t=time. Initially, the specific surface area of an aerosol is a function of its constituents' size distribution and shape. However, the specific surface area of particles changes as dissolution progresses, such that S becomes a function of time.

Both the specific surface area and crystallinity are dependent on process history. Changes in specific surface area of industrial uranium compounds with thermal treatment have been studied extensively [Landspersky and Vachuska 1966; Woolfrey 1976]. Since specific surface area is dependent upon process history, it is reasonable to say that solubility is therefore dependent upon process history.

Another factor affecting the dissolution rate of inhaled uranium aerosol is the role played by the alveolar macrophage. The macrophage is known to phagocytize uranium particles and to participate in clearing the lungs of particles after inhalation exposure [Andre *et al* 1989, Tasat and de Rey 1987, Batchelor *et al* 1982]. Particles are transported to the pulmonary lymph nodes (described below).

The nature of the contaminating aerosol determines the response of alveolar macrophages. Their response to soluble compounds proceeds by phagocytosing particles and dissolving them with their lysosomes [Andre *et al* 1987, Berry *et al* 1978, Kreyling *et al* 1986, Kreyling 1992, Lundborg *et al* 1985, Marafante *et al* 1987, Poncy *et al* 1992]. Alternatively, certain water-soluble components can enter the macrophages in the form of ions, concentrate in the lysosomes, and then precipitate in an insoluble form (uranyl phosphate) through the action of the lysosome acid phophotases [Berry *et al* 1993, Galle 1983]. This is the case, for instance, with uranium which, when inhaled as a soluble form of uranyl nitrate, concentrates and turns into insoluble needles of uranyl phosphate in the macrophage lysosomes [Henge-Napoli *et al* 1996]. Parenthetically, this phenomenon was also observed in other cell types (intestinal cells, kidney cells, liver cells, bone cells and bone marrow cells) and for metals such as aluminum [Berry *et al* 1982], gallium, indium, uranium [Galle 1982] and niobium [Galle and Berry 1980]. This protects the alveolar environment from the toxic effects of the uranyl ions and limits their transfer into the organism through the alveolocapillary membrane.

Additionally, macrophages play an active role in uranium transport beyond lung tissue proper: Leach *et al* [1970, 1973] found black uranium pigment within the tracheobronchial lymph nodes following chronic inhalation. On occasion, necrosis of the lymphoid tissue was observed [Leach *et al* 1970]. It has also been suggested that macrophage scavenging is responsible for accumulation of uranium in the spleen following inhalation [Pellmar *et al* 1999a].

To summarise, inhalation is the most probable route of uranium dust entering the body. Large dust particles will be expelled from the lungs and swallowed, whereas smaller particles could reach the alveoli. The solubility of particles in the alveoli will be governed by the chemical properties of the uranium: salts dissolve quickly (days), and oxides dissolve slowly (years). Finally, the body's immune system (alveolar macrophages) can accelerate the removal of uranium from the lungs.

3.2 Health Effects

Several studies have shown that inhalation exposure to highly enriched forms of uranium can result in damage to the lungs, namely changes to cell populations and histology. Morris *et al* [1992] exposed rats to enriched uranium dioxide (137-270 kBq/m^3 = 150-300 mg U/m^3) for 100 minutes. Alveolar fibrosis and other unspecified lung pathology were noted after 720 days. However, it is difficult to categorically differentiate between radiological and chemical damage in many of these experiments. For example, Leach *et al* [1970] exposed monkeys to aerosolised uranium dioxide (126 Bq/m^3 = 5.1 mg/m^3) for over three years, and noted changes in lungs and tracheobronchial lymph nodes due to *either* radiation or inorganic dust. Longer exposures resulted in pulmonary fibrosis, and lymph necrosis and fibrosis – but no renal damage was noted. The large radiation doses (approximately 10 Gy), the presence of lung and lymph node changes, and lack of renal damage suggests chronic radiation damage; however, similar changes in lungs have been observed following chronic exposure to (inorganic) dust [ATSDR 1999].

To study changes in cell populations, Morris *et al* [1992] exposed rats to aerosolised 92.8% enriched uranium dioxide (84.1 – 202 kBq/m^3) for 100 minutes (similar experiment described above). Eight days post-exposure, the authors noted increased numbers of lung macrophages, type I cells (which transfer substances from alveolar space to blood), and type II cells (which produce pulmonary surfactant and enzymes for pulmonary metabolism). In this experiment, the authors made an effort to identify whether changes were due to radiological or chemical toxicity. This was done by exposing a portion of the rat population to neutrons to deliver a dose that was 300x greater than the radiation dose from the uranium alpha particles. No significant difference was noted between the group exposed only to uranium dioxide vs. the group exposed to both uranium dioxide and neutrons. Since the neutron exposure caused no short-term pulmonary effects, the authors conclude that any observed *short-term* effect was due to chemical, rather than radiological, toxicity of the uranium.

In acute exposure cases, reports of pulmonary toxicity are limited to experiments using uranium hexafluoride in animal models. This chemical form of uranium reacts with water to produce hydrofluoric acid (and uranyl fluoride). Thus, animals exposed to uranium hexafluoride probably suffered from exposure to hydrofluoric acid, which promptly damages pulmonary tissue [Leach *et al* 1984, Stokinger *et al* 1953]. Acute inhalation experiments typically used massive exposures (hundreds to tens-of-thousands of milligrams of uranium hexafluoride/m^3 [Leach *et al* 1984] over several minutes [Leach *et al* 1984]. Longer duration exposures, over months, are carried out using lower concentrations; typically tens of milligrams of U/m^3. In the case of

uranium hexafluoride exposure, evidence of pulmonary edema, emphysema, and bronchial and alveolar inflammation were noted in rats, mice, and guinea pigs [Spiegl 1949].

As indicated above, less-soluble uranium compounds (Class S) are retained by the lung or slowly cleared by mucoscilliary mechanical processes. The lung therefore becomes the principle target organ for inhaled insoluble uranium compounds that are retained for long periods of time. However, Leach *et al* [1970] did not find evidence of lung damage in either rat or dog models following 1-5 years of exposure to uranium dioxide dust (5 mg U/m^3). Further, Cross *et al* [1981a,b] conducted a study with a variety of animal models (dogs, rats, rabbits), and did not find uranium-induced histological lung damage after 7-13 months of exposure to 0.05-10 mg U/m^3 aerosols.

For high concentrations over a long period of time, exposure could induce lung cancer. For example, Leach *et al* [1970, 1973] used a beagle model to show that after chronic inhalation exposure of 5.8 mg uranium dioxide / m^3 for 5 years, dogs accumulated a steady state concentration of 2 mg uranium / g lung (and a body burden of 16 mg uranium / kg body mass). The lungs accumulated 6.6 Gy radiation dose leading to primary tumors (pulmonary lymphatic neoplasms and increased epithelial proliferation) in four animals at the end of the study. However, the authors noted that these findings may not extrapolate well to humans, since these pathologies are rare in humans [Leach *et al* 1973].

Dupree *et al* [1995] conducted a study of lung cancer among uranium workers in four processing plants: two Tennessee (Oakridge; Y-12 and K-25), one in Missouri (Mallinckrodt Chemical Works Uranium Division Fernald), and one in Ohio (Feed Materials Production Centre). Workers were primarily exposed to insoluble uranium dust. The authors found, through a dose-response analysis, that uranium cumulative exposure of up to 25 cGy does not increase lung cancer risk, and that there are too few cases above 25 cGy to determine whether or not an increased risk exists.

As indicated earlier, uranium is known to accumulate in lymph tissues following pulmonary exposure. A possible consequence of chronic accumulation of uranium in the lymphatic (and skeletal) system may be compromised immune function [Pellmar *et al* 1999a], but this has not been demonstrated. Tracheobronchial lymph nodes accumulate insoluble particles translocated from the lung, but do not appear to be as sensitive to radiation as lung tissue and are not generally considered to be a target organ for uranium toxicity. However, at high concentrations over several years, some effects have been observed: Leach *et al* [1970] noted infrequent patchy hyaline fibrosis in the tracheobronchial lymph of dogs and monkeys after three years of exposure to uranium dioxide dust (5 mg U / m^3 for 5.4 hours a day, 5 days a week). On occasion, necrosis of the lymphoid tissue was observed. In a human population, Frome *et al* [1990] conducted a study of 28008 uranium workers from Tennessee (Oak Ridge) (part of this group overlapped with the study by Dupree *et al* [1995] cited above). Here, the authors observed 40 deaths from lymphatic cancer (48.23 deaths were expected). This was the largest study found and figures here do not suggest a relationship between lymphatic cancer and uranium. However, this form of cancer is

difficult to study because it is rare, and more research is needed to confirm or refute these findings.

4. DERMAL EXPOSURE

4.1 Modes of Entry

The skin is considered to be a significant route of entry for uranium into the body, primarily due to the skin's large exposed surface area [Bartek *et al* 1972]. Skin contamination of workers directly engaged in uranium processes can be considered as a highly probable occupational risk [Orcutt 1949, De Rey *et al* 1984]. Skin contact with powders or liquids containing uranium, whether directly through contaminated clothing or accidentally through broken gloves, makes the percutaneous route of particular relevance to the workers involved in the industrial processing of uranium and its compounds [Hodge *et al* 1973, Stradling *et al* 1991].

4.2 Health Effects

Several animal studies have demonstrated that dermal exposure to high levels of soluble uranium can lead to negative health outcomes. Studies have shown that percutaneous absorption of soluble uranium compounds can damage skin and kidneys – the latter following uranium contamination of the circulatory system [De Rey *et al* 1983].

Lopez *et al* [2000] used a rat model to show that topical exposure to high concentrations of uranyl nitrate ($UO_2(NO_3)_26H_2O$), which is highly soluble, can induce death. Two experiments were performed. In the first, a negative correlation was observed between survival rate (33%, 29%, 67%, 83%, and 80%) and the size of an area treated with a 0.6 g / mL uranyl nitrate water-oil solution (6, 4, 2, 1, and 0.5 cm^2, respectively). The second experiment showed a strong dependence between survival rate of the rats and the time of exposure to a 0.6 g / mL uranyl nitrate solution on an area of 8 cm^2. The survival rate for animals exposed for 1, 7, and 15 min was 100%; 67% for 30 min; 45% for 1 hour; 43% for 3 hours; 10% for 8 hours; and 0% for 24 hours. The authors found that renal vascular congestion increased with exposure and attributed death to chemical – rather than radiological – toxicity.

There is limited evidence of dermal effects in animal models; however, dermal effects of uranium in humans have not been reported [IOM 2000, ATSDR 1999]. Although there are no recommended maximum allowable concentrations for uranium exposure of the skin, the levels that resulted in pathological effects in animals are very high. Currently, there is insufficient literature available to conclusively demonstrate the presence or absence of health risks associated with dermal exposure.

5. GASTRIC SYSTEM EXPOSURE

5.1 Absorption

Several groups have shown gastric absorption to be minimal. For example, in the experiment by Pellmar *et al* [1999a] (see Section 2), although approximately 1.100 μg uranium / g feces was found in all rat groups (controls, low, medium, and high uranium exposure), there was no observed dose dependence. The authors attribute these uranium levels to result from the intake of uranium through the food and water, which contained uranium concentrations of 0.360±20 μg uranium / g and 0.25±0.05 μg uranium / L, respectively.

There is some debate regarding gastric absorption kinetics. The ICRP has estimated gastrointestinal absorption (f_1) to be 5% [ICRP 1988]; this has been used to calculated internal doses due to uranium entering the body through this pathway. Leggett and Harrison [1995], however, note that this is an overestimate and suggest 1 - 1.5% is a better estimate of gastrointestinal absorption. Karpas *et al* [1998] studied the gastrointestinal uptake of uranium following a low-concentration acute intake in a human model. Five volunteers ingested a drink spiked with 100 μg of uranyl nitrate, and the level of uranium in their urine after ingestion was monitored. The results indicate that the urine uranium excretion is maximal approximately 6-10 hours following ingestion. The uptake fraction was measured to be 0.1 - 0.5% of the ingested uranium for four of the subjects but 1.5% for the fifth, which is well below the 5% reported by the ICRP.

5.2 Health Effects

Even in cases of massive overexposure involving ingestion of tens of grams of highly soluble uranium, ingestion of uranium has not been found to be associated with clinically significant gastrointestinal disorders [Pavlakis *et al* 1996]. However, there are still too few studies of this exposure route to determine if any associated risks to the gastrointestinal system exist.

6. SKELETAL EXPOSURE

6.1 Modes of Entry and Retention Mechanisms

Animal studies [Ballou *et al* 1986, Diamond *et al* 1989, La Touche *et al* 1987, Morrow *et al* 1982, Neumann *et al* 1948, Voegtlin and Hodge 1949, Walinder 1989] and epidemiological assessments [Kathren *et al* 1989, Singh *et al* 1987] demonstrate that the skeleton is a primary reservoir for uranium regardless of the route of exposure. Dang *et al* [1995] have reported that for chronic intake by humans, uranium content can be greater in the skeleton than in any other tissue measured, and that the concentration is about 70% of that in the kidney. This affects the time course of uranium exposure in other organs. For example, in experiments that follow the effect of a single uranium (intravenous) dose, the uranium originally deposited in the skeleton is released back into the blood. This (continually declining) deposition of uranium back into the blood, in turn, affects the time curve of uranium concentration in the kidney, extending it further in time than would otherwise be expected [Morris and Meinhold 1995]. The ICRP [1995] present a recycling model to describe the kinetic behaviour of uranium in humans. This assumes deposition in the mature skeleton to account for 15% of the activity leaving the blood, with trabecular:cortical bone surface deposition being in the ratio of 1:1.25.

There is some evidence that uranium deposited onto the bones is similar to calcium. Like calcium, uranium will deposit on all bone surfaces; this deposition is increased in regions of active growth or remodelling, where the uranyl ion $[UO_2]^{2+}$ can displace Ca^{2+} [Arsenault and Hunziker 1988, Neuman *et al* 1949]. Although uranium has been shown to gradually diffuse into bone [Stevens *et al* 1980, Rowland and Farnham 1969]; it does not enter the hydroxyapatite lattice [ICRP 1995].

Pellmar *et al* [1999a] studied uranium distribution using a rat model (see Section 2) The authors demonstrated that bone, teeth and lower jaw contained high levels of uranium when measured 18 months after uranium implantation.

Estimates for the time of uranium removal from the bone surface range from about one month to more than one year. Taylor *et al* [2000] indicate that removal time from bone surfaces is approximately 5 days: half of the removed uranium returns to the plasma, and half enters an exchangeable bone compartment, from which it is removed with a half-life of 30 days. Another report indicates that the half-life of uranium in bone is approximately 300 days [Harley *et al* 1999]. Human data [Bassett *et al* 1948, Bernard *et al* 1957, Luissenhop *et al* 1958] suggests that 80% to 90% of a skeletal deposit of injected uranium is lost within about 1.5 years.

6.2 Health Effects

Several studies have shown skeletal toxicity caused by high doses of uranium exposure. Guglielmotti *et al* [1984] demonstrated inhibition of bone formation, and ascribed this to depletion of active osteoblasts. In later experiments, Ubios *et al* [1995, 1998] observed alterations in mandibular growth in rats following either intraperitoneal injections or percutaneous absorption of uranyl nitrate (one administration of 2 mg/kg body mass).

Because uranium has a medium to long residency time in bone, it is conceivable that uranium may present a carcinogenic risk. Ritz *et al* [1999] conducted a study of 4014 workers at an Ohio Uranium processing plant, and found no deaths due to bone cancer (where 0.99 were statistically expected). Several authors suggest that sufficiently enriched uranium can deliver an accumulated radiation dose sufficient to be considered a radiological risk [Morrow 1986; Stannard 1988]. However, in a study of 28008 workers at a uranium enrichment processing plant in Tennessee (Oak Ridge), Frome *et al* [1990] noted 11 deaths due to bone cancer (where 10.35 were statistically expected). In neither study were differences between actual deaths and expected deaths statistically significant. Bone cancer is a rare disease, and there are still too few studies to determine whether or not it can be induced by uranium.

7. LIVER EXPOSURE

7.1 Modes of Entry

The liver has been shown to accumulate uranium following internal contamination Pellmar *et al*'s [1999a]. In this study, rats were implanted intramuscularly with uranium pellets (see Section 2). As early as six months post-implantation, the concentration of uranium in most organs was found to be well-correlated with the amount of implanted uranium. Notable exceptions were the liver and spleen where no correlation was noticed until 12 or 18 months post-implantation, suggesting very slow or variable uptake kinetics. However, trace quantities were detected in these two organs as early as 1 day post-implantation.

7.2 Health Effects

Despite the acknowledged possibility of uranium accumulation in liver, no significant liver dysfunction has been reported in animal or human studies. For example, Stokinger *et al* [1953] did not find liver dysfunction in a study of inhalation effects where animals were exposed to uranium trioxide (10 mg/m^3) for two years. In human studies, Pavlakis *et al* [1996] studied one case of deliberate ingestion of 15 g of uranium acetate. Liver function was reported normal from initial investigation to six months following intoxication. Similarly, Lu and Zhao [1990] report that normal liver function was observed in an individual three years following exposure to uranium tetrafluoride.

The liver is acknowledged to be an important accumulation point of uranium. Although no study has demonstrated hepatotoxicity, currently there is still insufficient information to completely refute a relationship between liver dysfunction and uranium intoxication.

8. NERVOUS SYSTEM EXPOSURE

8.1 Modes of Entry and Retention

Several studies have demonstrated that uranium does distribute into the nervous system. The neurotoxicity associated with exposure to other heavy metals (eg., lead and mercury) suggests the potential of neurophysiological and behavioural consequences of uranium accumulation in the brain with chronic high-dose exposure.

Pellmar *et al* [1999a] used a rat model to determine distribution of (depleted) uranium following long-term exposure to intramuscularly implanted fragments (see Section 2). Three doses were assessed: low dose consisted of four uranium pellets and sixteen tantalum, medium dose: ten uranium and ten tantalum, and high dose: sixteen uranium and four tantalum. A dose-dependent increase of uranium was observed in the homogenized hemisphere of the rat brain six months after implantation. Rats sacrificed eighteen months post-implantation showed different concentration of uranium in different parts of the brain; such non-uniform distributions have been seen with other heavy metals [Butterworth *et al* 1978, Cholewa *et al* 1986, Ono *et al* 1997, Rios *et al* 1989, Ross *et al* 1996]. Further, uranium bound to blood did not account for the levels found in the brain, suggesting that uranium can cross the blood-brain barrier.

8.2 Health Effects

In a study by Pellmar *et al* [1999b], a rat model was used to examine electrophysiological changes associated with imbedded uranium fragments. All rats received twenty 1mm x 2mm cylindrical pellets (10 in each thigh), as described in the prequel study by the same group [Pellmar *et al* 1999a] (see Section 2). After 6, 12 and 18 months, rats were euthanized, hippocampi removed and electrophysiological potentials analyzed by extracellular field potential recording. In the six-month group, synaptic potentials in the uranium-exposed groups were less capable of eliciting spikes. There was no demonstrable dose-dependence. By eighteen months after implantation of the metal fragments, control tissues and uranium-exposed tissues were not significantly different from each other (any remaining effects may have been obscured by ageing). No nephrotoxicity was observed.

Currently, there is some debate as to whether any observed alterations in neural response are a result of direct uranium-neuron interaction, or uranium affecting neural response via altered electrolyte concentrations. For example, Uranium has been shown to induce electrophysiological changes in central and peripheral nervous systems. Lin *et al* [1988] has demonstrated *in vitro* that the uranyl ion can enhance mouse muscle contraction with acute local concentrations (200-400 μM). The authors indicate the effect was potentiated by low concentrations of extracellular calcium and antagonized by high concentration of extracellular calcium.

However, Pellmar *et al* [1997] suggested neurological changes secondary to electrolyte imbalance to be unlikely. In a precursor to the 1999[b] rat-model study, they found significant accumulation of uranium in the kidney (5123±259 ng/g with high dose uranium) and excretion in the urine (1009±87 ng/ml with high-dose uranium at 12 months). Again, a preliminary evaluation [Pellmar *et al* 1997] did not indicate any nephrotoxicity. Even at the high dose of uranium, urine lactate dehydrogenase, protein, glucose, N-acetyl-BETA-glucosaminidase, creatinine clearance and fractional excretion were not altered after 6 and 12 months of exposure. The uranium accumulation in the hippocampus, on the other hand, was significant at 18 months after the pellet implantation, suggesting the possibility of direct effects of chronic uranium exposure in the central nervous system. However, the mechanism by which uranium could cause any neurophysiological changes is unknown.

The mechanism by which uranium enters the neural system is unknown, and may be different from that used by other metals. Lead has been hypothesised to enter the terminal through the calcium channel and once internal to the presynaptic terminal can act as a calcium agonist to promote transmitter release [Wang and Quastel 1991]. Disruption of calcium mechanisms is a common action of the heavy metals [Wang and Quastel 1991, Farnell *et al* 1985] that may underlie altered neurophysiological properties. However, Lin *et al* [1993] used a calcium channel blocker (on a Chinese hamster ovary cell model) to show that uranium may not enter through calcium channels.

Reports have been inconsistent regarding *in vivo* neurological/behavioural effects following uranium exposure. Domingo *et al* [1987] demonstrate that oral and subcutaneous administration of relatively high doses of uranyl acetate elicits tremors in rats. Conversely, Pellmar *et al* [1997] used a rat model to show that no gross performance decrements were noticed in locomotor activity, discrimination learning, and general function. However, the authors concede that these behavioural measures are not sufficiently sensitive to reveal subtle cognitive deficits. In humans, Kathren and Moore [1986] report that normal mental function was acutely disrupted in three individuals accidentally exposed to a cloud of soluble uranium compounds. In one deliberate (suicidal) case, a 103kg man ingested 15g of uranium acetate, which resulted in acute drowsiness and slurred speech, but no observed focal neurological deficit [Pavlakis *et al* 1996]. In another case, a patient who handled a uranium bar for three years developed increased stool uranium, foot cramps, leg pain, and abnormal gait [Goasguen *et al* 1982]; however, in this study it was not clear whether symptomatology was related to uranium poisoning. The current status of the above patients has not been reported.

In McDiarmid *et al*'s [2000] study of Gulf War veterans possessing retained fragments of depleted uranium, two neurocognitive tests were performed: a traditional evaluation, and an automated (computer administered) evaluation. The automated evaluation demonstrated (1) a statistically significant difference in neurocognitive test performance between exposed and non-exposed veterans ($P<0.01$), and (2) a significant correlation between urine uranium levels (24 hour sampling) with test scores ($P<0.01$). However, traditional testing did not find either significant. The authors indicate that the number of individuals with elevated uranium values was small

and a few veterans had complex histories that may have contributed appreciably to the observed variance.

In short, although uranium has been shown to cross the blood brain barrier, it has not been shown to effect locomotor activity or discrimination learning in rats, and effects in humans have not been convincingly demonstrated. Thus, it is difficult to determine the impact of increased levels of uranium on neurological function.

9. REPRODUCTIVE SYSTEM EXPOSURE

9.1 Absorption and Retention

Pellmar *et al* [1999a] used a rat model to study the distribution of uranium in animals implanted with uranium pellets (see Section 2). At 18 months post-implantation, the authors found a dose-dependent increase of uranium in the testicles: approximately 0.2 and 0.6 μg U / g tissue for rats implanted with 10 and 20 uranium pellets, respectively.

McDiarmid *et al* [2000] included semen testing for uranium in their study of the health effects of uranium on exposed Gulf War Veterans. The authors report that 5 of 22 subjects had semen concentration above the limit of detection (1.1 ng / g ejaculate); all samples with detectable levels were from the group of veterans that were exposed to uranium.

9.2 Health Effects

Some studies suggest that chronic uranium exposure in males has the potential to affect reproduction [Llobet *et al* 1991, Malechenko *et al* 1978, Muller *et al* 1967]. For example, in a study by Llobet *et al* [1991], male mice were exposed to high doses (up to 80 mg / kg per day) of uranyl acetate over 64 days. A decreased pregnancy rate was found in females that were mated with the exposed male mice; however, this decreased pregnancy rate was not dose-dependent. The authors did not find evidence of impaired testicular function and spermatogenesis, even at very high exposures. Regarding human effects, male uranium miners were found by one study to have more female offspring than predicted [Muller *et al* 1967]. In McDiarmid *et al*'s [2000] study, semen characteristics including physical parameters (volume, count, and concentration) and motility (percentage motile and progression and motion) were analysed comparing high with low uranium exposure groups. The authors report no observed uranium effect.

There is very little data available concerning the effects of uranium on the reproductive system, and many authors acknowledge the need for further investigation before any association can be made or refuted between uranium exposure and reproductive disorders.

10. KIDNEY EXPOSURE

10.1 Retention and Excretion

The chemical form of uranium is an important factor in determining initial absorption by any route. However, once uranium enters the circulatory system, it complexes with bicarbonate, and this complex determines all subsequent behaviour. Upon entering the kidney, the uranium bicarbonate complex has been shown to dissociate in the acidic conditions of the proximal tubules, leaving the free uranyl ion to attach to protein of the tubular epithelial cells [Stannard 1988].

Data from uranium injection experiments on humans and animals shows that a significant fraction of the uranium filtered by the kidneys is temporarily retained in the renal tubules before excretion to the bladder. For example, ICRP [1995] reports that in humans, dogs, and rats, the kidney contained 12-25% of injected uranium at 1-3 days post-injection. Durbin *et al* [1986] found that 92-95% of injected uranium was excreted with a half-life between 2 to 6 days; the rest being removed with a half-life between 30 and 340 days.

In a study by Pellmar *et al* [1999a] uranium pellets were surgically implanted at three dose levels (see Section 2). As early as one day post implantation, the concentrations of uranium in the urine of medium and high-dose rats were significantly different from the Tantalum controls. Urinary uranium concentration reached a maximum at 12 months: 1.010±0.087 μg U / ml urine for high-dose, and 0.224±0.032 μg U/ml urine for low-dose.

Hooper *et al* [1999] studied elevated urine uranium excretion from veterans with retained uranium shrapnel. Thirty-three individuals were studied during 1993/4 (time 1) and 1995 (time 2): 23 reported they had been told they were wounded by shrapnel (but were not sure if it had been removed during early wound treatment). Fifteen of the 23 had shrapnel present (as identified by x-ray), while no shrapnel was seen on the remaining eight. Although some shrapnel pieces were as large as 20 mm, most individuals had many fragments less than 1 mm scattered throughout muscle tissues. The authors observed that for the 1993/4 (time 1) period, the average urinary uranium was significantly higher in veterans with confirmed retention of metal fragments compared to those without metal fragments: 10.08 μg U / L urine versus 0.07 μg U / L urine (or 4.47 versus 0.03 μg/g creatinine). The same observation was made for the 1995 (time 2) urine samples: 18.20 μg U / L uranium for veterans with confirmed shrapnel versus 0.04 μg U / L urine for veterans with no suspected shrapnel (6.40 and 0.01 μg / g creatinine, respectively). Based on these observations, the authors suggest that the uranium fragments are biologically active. Average urine uranium concentration in unexposed individuals ranges from 0.004 to 0.0128 μg U / L urine [Medley *et al* 1994]. Additionally, the authors compared spot urine collections with 24 hour sampling, and found that spot urine samples in which uranium concentration are normalised to creatinine can be used to predict 24-hour uranium excretion, which was

later confirmed in the follow-up study by McDiarmid *et al* [2000], below. Parenthetically, normalisation to creatinine accounts for body hydration and has been proposed to control for diurnal variability and large inter-individual variability observed in non-exposed subjects [Karpas *et al* 1998].

The same group of veterans was re-examined in 1997 by McDiarmid *et al* [2000]. The results of 24-hour urinary uranium measurements were: between 0.01 and 30.74 μg / g creatinine for the uranium-exposed group, and between 0.01 and 0.047 μg / g creatinine for the non-exposed group. The authors state that the high correlation between uranium in these results and those from Hooper *et al*'s [1999] study using data from 1994 and 1997 reveal a "persistent, steady-state excretion of uranium [suggesting] that excretion is not significantly lowering the body burden of uranium in those with retained metal fragments".

Urinary excretion is the principal avenue of removing uranium from the body. Since kidney function determines excretion kinetics and impaired function could therefore alter such kinetics, it becomes important to understand how kidney function is perturbed by uranium exposure. Kidney damage could affect the overall retention and deposition throughout the body, especially the retention and deposition of uranium acquired subsequent to the appearance of substantial kidney lesions.

In summary, the kidney is the principle route of uranium excretion from the body. Data from animal models and veterans shows that intramuscularly-imbedded uranium fragments results in elevated uranium levels in urine. Veteran data indicates that elevated levels of urinary uranium are persistent for at least tens of years.

10.2 Health Effects

The degree of renal injury has been found to be dependent on species, dose, chemical form, and route of administration. In general, several authors have noted both proximal tubular and glomerular changes (however, the glomerulus is not the principal target of uranium [Hodge *et al* 1973]). Glomerular changes include damage to basement membranes, which results in decreased reabsorption of sodium and decreased clearance of inulin and creatinine [Stopps and Todd 1982]. In experiments using a rat model, Lopez *et al* [2000], studied renal effects following topical application of uranyl nitrate (0.6 g /mL $UO_2(NO_3)_26H_2O$ in an water emulsion). Histological analysis of the kidneys of rats exposed to uranyl nitrate applied to 1 cm^2 of skin for 30 minutes showed vascular congestion and vacuolization of the tubules in the corticomedullar boundary. For groups with exposures for longer duration or over a larger area, histological analysis revealed hyaline bodies and necrotic areas. Damage to proximal tubules results in increased excretion of enzymes and sloughing of casts containing necrotic cells [Berlin and Rudell 1986]. In cases of very high dose, renal damage could result in death (even following percutaneous absorption[de Rey *et al* 1983, Marzorati *et al* 1990]).

Gilman *et al* [1998] used a rabbit model to investigate the effect of exposure to uranyl nitrate hexahydrate ($UO_2(NO_3)_2{\cdot}6H_2O$) in drinking water over 91 days. Rabbits

received drinking water with the uranium compound added to form concentrations of 0.96, 4.8, 24, 120, or 600 mg/L (controls ingested less than 0.001 mgU/L). The study used 10 males and 10 females per group; males and females were analysed separately. In males and females, after 91 days of exposure, urinary parameters (glucose, creatinine, urea nitrogen, total protein, albumin, lactic dehydrogenase, gamma-glutamyl transpeptidase, leucine aminopeptidase, and N-acetyl-beta-D-glucosaminidase) did not show statistically significant changes. Histopathological changes were observed at the lowest and highest exposure levels both to the glomeruli and tubular epithelial cells, as well as the renal interstitium. The authors found that female rabbits appeared much less affected by the exposure regimen than males. Female rabbits consumed approximately 65% more water than males, making their uranium intake approximately 50% greater on a [mg/(kg body mass)/day] basis. However, female tissue uranium levels were not similarly raised for the highest exposure group: for example, the average kidney uranium level in females was only 20% of that in males, and bone uranium level in females was 76% of that in males. This suggests the possibility that (1) male and female rabbits have different pharmacokinetic parameters, and/or (2) increasing fluid consumption reduces the amount of uranium present in the body and histological manifestation of uranium toxicity. Interestingly, similar effects have been noticed for other metals; for example, it is well established that the rate of clearance of caesium is faster in females than in males, and also that clearance may be further accelerated during pregnancy [Melo *et al* 1997, ICRP 1989].

Regarding studies of uranium-induced kidney damage in humans, Russell *et al* [1996] performed a post-mortem kidney pathology study of seven workers who were in the uranium industry for at least 15 years and had urine samples throughout the course of employment. Work was typically with various enrichments of uranium varying from depleted (0.2% ^{235}U) to a few percent ^{235}U. Six adult controls were used who had no occupational history of uranium exposure. For the exposed group, mass concentrations of kidney uranium ranged between 0.4×10^{-3} μg/g kidney to 0.249 μg/g kidney, urinary uranium concentration ranged from undetectable to 110 μg/L, and total uranium passing through kidneys over the worker's lifetime (retrospectively calculated) ranged from incalculable to hundred of milligrams. The authors found that none of the uranium workers in this study showed histological changes attributed to uranium neuropathy – which was reasonably expected since the traditional tissue threshold is considered to be 3 μg / g kidney [See Chapter 10.3].

Similarly, in studies of Gulf War Veterans with embedded depleted uranium shrapnel, no evidence of renal injury was found (including markers of proximal tubular insult), despite uranium urinary excretion thousands of times higher than non-exposed veterans [McDiarmid *et al* 2000, Hooper *et al* 1999]. The exposed veterans' lifetime occupational exposures, however, were generally much lower than the uranium workers studied by Russell *et al* [1996].

Significant kidney damage was diagnosed in one incident, involving a single deliberate overexposure of uranium (ingestion of 15 g of uranyl acetate) [Pavlakis *et al* 1996]. Upon initial hospitalisation, the individual presented evidence of an incomplete Fanconi syndrome, manifesting as a renal tubular acidosis. This condition persisted in

a follow-up examination 6 months after the incident, and is being treated daily with sodium bicarbonate.

Although humans have a long history of involvement with uranium, kidney pathology associated with uranium intake in humans is only poorly understood – especially for low-level chronic exposure. Few reports have appeared describing functional renal impairment following the handling of various occupational forms of uranium [Thun *et al* 1985, Lu *et al* 1990]. The animal data describing renal damage from uranium is more extensive than human data. The human data has been inconclusive in documenting abnormalities in renal function in exposed groups.

10.3 Threshold of Health Effects

As a results of uranium accumulation, the kidney is the critical target for uranium toxicity [Diamond 1989, Diamond *et al* 1989, Kocher 1989, Leggett 1989], but it is a less potent toxin than the classical nephrotoxic metals (such as mercury and lead) [ATSDR 1999]. However, an important issue that is seldom addressed is: at what point should an effect be considered significant? Wrenn *et al* [1987] describe four stages of effect: biochemical change, histological change, chronic poisoning, and acute poisoning. The Nuclear Regulatory Commission classifies effects as: no effect, transient renal injury, and permanent renal damage [McGuire 1991]. It has been suggested that 3 μg uranium / g kidney be a threshold below which serious damage of occupationally exposed individuals would be prevented [Rich *et al* 1998]. However, animal experiments indicated mild renal injury at lower kidney concentrations (less than 1 μg uranium / g kidney) [Leggett 1989, Gilman *et al* 1998]. Various estimates for a threshold have been published for rats, suggesting approximately 0.7-1.3 μg U / gram kidney, where much more marked injury is observed in the range 1.3-3.5 μg uranium / gram kidney. [Diamond *et al* 1987]. A threshold estimate of 0.3 μg / g kidney has been reported in dogs [Morrow *et al* 1982]. Gilman *et al* [1998] reported a lowest observed adverse effect of 0.04 μg uranium / g kidney in a rabbit model.

It may be important to address differences in acute and chronic exposure. Research groups studying uranium effects on the kidney have considered both acute and continuous uptakes. Generally, acute uptake protocols involve intravenous injection of a soluble uranium compound, whereas continuous uptake protocols can involve surgical implantation of a uranium compound with slow dissolution kinetics, or ingestion of uranium dissolved in water. Continuous intake of uranium could produce a deposition pattern in the kidney that is different from the deposition pattern resulting from a single intravenous injection [Lloyd *et al* 1996]. For example, Stevens *et al* [1980] have shown that in the case of an acute intake into blood, only a portion of nephrons become labelled with uranium, perhaps because only a fraction of the nephrons are active at any one time. Continuous exposure to uranium could result in a more uniform deposition in the nephrons – extending damage effects over a larger portion of this tissue.

Animal studies of acute low-level uranium exposure have shown kidney repair [Morris and Meinhold 1995]. However, original cells may be replaced by cells with

different characteristics, but the same apparent function. For example, damaged tubular epithelial cells are replaced by atypical cells, which were originally thought to be more tolerant to subsequent uranium insult. However, recent studies of chemical neuropathy have demonstrated that uranium "tolerance" is most likely the result of a histologically deranged kidney with abnormal physiology [Russell *et al* 1996]. Minor damage arising from low-level acute exposure may not lead to degraded function, but simply to a reduction in the kidney's reserve capacity. Of course reduction of reserve is not as important as an immediate reduction of function; however, a depleted reserve capacity may ultimately compromise function if such a reserve is challenged to a recruitment resulting from an independent insult. Kathren and Weber [1988] suggest that this is why no effect has been observed among thousands of uranium workers exposed under the limit of 3 μg U / g kidney. Leggett *et al* [1989] has proposed that this guidance level for limiting human occupational exposure should be lowered to approximately 0.3 μg U / g kidney. However, it is important to note that this figure is based on extension of animal experiments to humans. Except in cases of massive overexposure in humans [Pavlakis *et al* 1996], uranium has not been shown to cause clinically significant perturbations of renal function.

11. MUTAGENIC POTENTIAL

A number of studies have demonstrated that uranium compounds have mutagenic and carcinogenic potential, but the implications for long-term human exposure is still unclear.

Miller *et al* [1998] used a model of *in vitro* human osteoblast cells to compare the transforming potential of uranyl chloride (UO_2Cl_2) with nickel sulphate or lead acetate – known to be biologically reactive and carcinogenic. They report the ability of uranyl chloride to transform the osteoblasts to their tumorigenic phenotype after 24 hours of exposure. These transformants were characterised by anchorage-independent growth, elevated expressions of the k-ras oncogene, reduced production of the Rb tumour supressor protein, elevated levels of sister chromatid exchanges per cell, and tumour formation in nude mice implanted with the cells. Compared with other metals: the uranium compound was 1.49 times more potent than nickel sulphate and 2.02 times more potent than lead acetate in elevating morphological transformation frequencies at equivalent concentrations (10μM).

The authors used Monte Carlo simulations of internal and external cellular uranium concentration to determine that only approximately 0.0014% of cell nuclei were hit by alpha particles; this argues for a negligible effect for radiation from the uranium. However, an important limitation to this study is that is does not account for the number of hit cells that have carcinogenic potential following a survivable mis-repair.

The negligible role for radiation was also reached by Lin *et al* [1993], who evaluated the genotoxic and cytotoxic potential of uranyl nitrate *in vitro*. In their experiment, Chinese hamster ovary cells were exposed to uranyl nitrate water concentrations ranging between 3 to 300 μM for 2 hours. Cytotoxicity and genotoxicity were confirmed at concentrations ranging from 10 to 300 μM: viability analysis showed 50% inhibition at 49 μM, an increased number of binucleated cells with micronuclei was found at concentrations greater than 100 μM, cell proliferation was inhibited above 10 μM, and chromosomal effects were noticed above 10 μM (sister-chromatid exchanges, and topological aberrations including dicentrics, breaks, and rings).

In another experiment, Miller *et al* [1988] assessed the potential mutagenic effects of long-term exposure to internalised uranium using a rat model. Rats were implanted with 2 mm long uranium pellets in their gastrocnemius muscle: either 4, 10, or 20 pellets. Tantalum, a metal commonly used in prosthetic devices and known to be biologically inert, was used as a control. Urine and serum was collected following 6, 12 and 18 months of exposure, and tested for mutagenic potential using the Ames Salmonella reversion assay. Results argue for a correlation between uranium concentration and mutagenic potential. Both urine uranium concentration and urine mutagenicity increased up to 12 months, and at 18 months both simultaneously levelled off or decreased (in contrast with tantalum, which did not show enhanced mutagenic activity). Serum contained neither uranium nor tantalum, nor showed mutagenic enhancement. The mutagenic pattern indicates both frameshift and base

pair substitutions to varying extents, depending upon the length of time after implantation and number of uranium pellets. Urinary uranium concentration ranged between 48±14 and 1002±80 ng / μmol creatinine. Parenthetically, the authors did not note any abnormal kidney pathology or pre-cancerous lesions.

McDiarmid *et al* [2000] performed a comprehensive evaluation of the clinical health effects of depleted uranium exposure in Gulf War veterans compared with non-exposed Gulf War veterans. An assessment of genotoxicity was included in this study: chromosomal aberrations and sister chromatid exchanges were measured from peripheral blood lymphocytes. However, neither uranium-exposed nor non-exposed groups were found to be different from other control populations.

Several preliminary animal and *in vitro* studies have shown that uranium may have genotoxic effects due to its chemical properties at very high concentrations however, no evidence to support this has been found in human populations exposed to uranium. More studies are needed to determine whether or not there is a relationship between uranium exposure and genotoxic effects in humans.

12. FUTURE DIRECTIONS

12.1 Biomarkers of Uranium Exposure

Uranium could distribute to many tissues following exposure; the rate depending upon the chemical and physical forms of the uranium and location of exposure on the body. Many groups have put effort into developing bioassays of exposure – the most popular being urinary testing. Soft and hard tissues could also be used as markers since uranium distributes to these tissues; however, this is often impractical for routine screening procedures.

Urine is an indirect - or surrogate - measure of body burden, and an important assumption made in urinary testing is that uranium exposure implies elevated urinary excretion. Hooper *et al* [1999] state that some individuals who *may* have had substantial acute inhalation exposure to depleted uranium (DU) are excreting uranium levels close to that of previously described unexposed populations – although exposure was *not* confirmed. McDiarmid *et al* [1999] recently compared urine testing between veterans who were *suspected* of having DU exposure versus veterans who were suspected of not having DU exposure. They found that the lower limit of urine uranium was similar for both populations (regardless of whether spot- or 24-hour samples were acquired, or whether measurements were normalized to creatinine). However, these results should be interpreted carefully. In follow-up studies, all veterans with *confirmed* DU shrapnel were found to be excreting levels of uranium above veterans with unconfirmed DU shrapnel (approximately 100 times higher) [Hooper *et al* 1999, McDiarmid *et al* 2000] (see Section 10.1). Further, analysis indicated that elevated urinary uranium persisted over two years for soldiers with confirmed DU shrapnel. Unfortunately, these studies restricted themselves to DU shrapnel, and did not address DU dust exposure. With regards to uranium dust exposure, Mitchel *et al* [1999] used a rat model to study inhaled uranium ore dust, lung clearance rates, and urine concentration, and found that uranium exposure did imply elevated urine uranium content.

A truly representative urine sample should be obtained by collecting all the urine excreted over a 24-hour period [Leggett 1994]. This is difficult to do in practice, and therefore testing often resorts to "spot" collection. However, spot collection is subject to enormous daily variability, and can lead to discrepancies of 5-10 times compared with 24-hour sampling for unexposed individuals [Karpas *et al* 1998, McDiarmid *et al* 1999], and discrepancies of 10 times for shrapnel-suspected individuals [McDiarmid *et al* 1999]. Some authors have suggested minimizing variability by accounting for the body's hydration status by normalizing urine uranium to urine creatinine [Karpas *et al* 1998], as is standard practise [Jackson 1966] for many other (toxic) heavy metals, such as cadmium, mercury, and lead [ATSDR 1999]. This has been shown to reduce variability, and better represent a 24-hour urine sample in both human volunteers [Karpas *et al* 1998] and veterans (exposed and non-exposed) [McDiarmid *et al* 1999]. Ultimately, the best method of urine collection is a 24-hour sample, normalized to

creatinine [Karpas *et al* 1998], which at least one author has used as a gold-standard [McDiarmid *et al* 1999].

Although uranium body burden might not imply elevated uranium excretion, no studies have been found that have demonstrated individuals with *confirmed* DU exposure excreting normal urine uranium levels. Unfortunately, it would be difficult to quantify uranium lung burden from urine testing because different uranium compounds have different solubilities (and therefore kinetics), and lung uranium compounds cannot be identified from urine testing. Thus, although urinary testing is useful as a first stage test, acting upon a positive diagnosis may require additional different testing to determine body burden.

A more direct measure of uranium body burden would be via whole- or partial-body gamma ray counting. Preliminary experiments indicate minimum detectable levels of approximately 0.5 mg of depleted uranium in a limb-sized phantom. Limited localization is achievable via differential attenuation of gamma rays having different energies (93 keV and 1 MeV) through soft-tissue [Kramer and Niven 1998]. Additional localization could be achieved through physical collimation, albeit at the expense of sensitivity [Quartuccio *et al* 2000]. Another possibility is using x-ray fluorescence to detect uranium (excitation via ^{57}Co gamma rays). Preliminary testing indicates that such measurements could qualitatively identify the presence or absence of uranium in subcutaneous fragments, but may not be sensitive enough to assess the metabolised bone-uranium from injuries in Gulf War Veterans [O'Meara *et al* 1998].

12.2 Studies of Toxic Effects

There are many aspects of uranium biological reactivity that remain unknown and require addition research, including – but not limited to – genotoxicity, carcinogenicity, neurotoxicity, kidney damage, and exposure thresholds for each. One of the most significant short-comings of published work, from a military perspective, is the lack of information concerning the health effects of exposure to forms of uranium that might be encountered in theatre. Most studies use left-over metal from DU ammunition *manufacturing*, which is 99.25% depleted uranium and 0.75% titanium by weight. For example, see studies by Miller *et al* [1998] or Pellmar *et al* [1999a].

One of the most common exposure scenarios would be to depleted uranium dust from *impacted* munitions – herein referred to as 'fired DU dust'. Fired DU dust contains a multitude of substances, including iron, titanium, vanadium, magnesium, manganese, and aluminum. Valuable studies would include: particle size spectra, chemical composition, elemental/isotopic identifications, and oxidation states.

No publications have been found concerning the health effects of fired DU dust. It is well-established that uranium solubility in bodily fluids are strongly dependent upon the chemical form of the uranium. The physical properties are also known to significantly affect absorption kinetics. Potential research should include studying fired DU dust solubility in pulmonary models.

Several preliminary studies have investigated uranium shrapnel solubility by studying intramuscular dissolution of depleted uranium alloy in rat models. A good way to build upon this work would be to investigate solubility of fired DU shrapnel, which, again, is expected to have different properties than DU alloy.

Sites of anticipated damage include lungs, kidneys, and liver; thus a histological study of these organs would be of value, in addition to urine analyses (eg. looking for casts, which are indicative of renal damage). Although some evidence of toxicity may be noticed following acute exposures (such as tissue necrosis), tests for carcinogenicity would require longer studies due to latency between exposure and disease manifestation. In any such studies, it would be important to include a comparison with depleted uranium alloy (found in unspent munitions).

12.3 Decorporation

Internal contamination by soluble uranium is extremely difficult to remove unless immediate interventional steps are taken. Uranium complexes with bicarbonate ions [Cooper *et al* 1982], which have been administered prophylactically after uranium exposure. Bicarbonate alkalizes blood enough to allow excretion of uranium through the kidneys. Although bicarbonate is often recommended as a chelator following internal uranium contamination [Stradling *et al* 2000a], experiments have shown it to be largely ineffective, and considering its side effects (hypokalaemia and alkalosis [Bhattacharyya *et al* 1992]) it would be useful to search for an replacement. Some alternatives have been suggested, such as Tiron and polyphosphonic acids; however, experimental data suggests that they too are largely ineffective unless administered immediately and at very high doses [Stradling *et al* 2000c]. Thus, at present, no effective chelating agents are available for uranium.

13. CONCLUSIONS

This document describes the current state of knowledge of the health effects associated with uranium exposure. Data was drawn from a broad spectrum of peer-reviewed scientific literature to summarise potential routes of uranium entry into the body, which organs are the principle targets for uranium toxicity, and known final health outcomes.

The risk of internalising uranium lies with its physical form, the solubility of its chemical form, and the site of entry into the body. Pulmonary exposure is considered to be the highest risk because lungs have a large surface area, while dust has a large surface area:mass ratio. Once inside the body, uranium will distribute through the blood. Although large portions of uranium will be excreted, there will be some accumulation in the kidneys, bones and liver.

The most probable potential health outcomes for uranium toxicity are kidney disease and cancer. Uranium probably does not induce clinically significant renal dysfunction, except in cases of massive overexposure (ingestion of tens of grams of highly soluble uranium) – where dysfunction is similar to classic heavy metal poisoning. Gastric absorption was found to be minimal following ingestion, and there have been no reported negative health consequences. Several *in vitro* studies and *in vivo* animal models have demonstrated dermal, mutagenic, neurological, skeletal and reproductive effects at very high concentrations of uranium exposure that can be created in laboratory conditions. Such concentrations are rarely encountered elsewhere, and these effects in humans have not been reported.

Most authors agree that uranium's most important potential for toxicity lies with its chemical properties – and not its radiological properties. Studies have shown that even veterans with embedded depleted uranium who are excreting uranium levels thousands of times higher than non-exposed populations are receiving radiation doses well below ambient background levels. Further, studies of tens of thousands of uranium mill workers, occupationally exposed at still higher levels over much longer periods of time, are showing no increases in cancer incidence. The most likely cancer forms are believed to be: lung, bone, and lymphatic cancer. With respect to pulmonary exposure – which is the most common scenario – cumulative exposure up to 25 cGy probably does not increase the risk of lung cancer. Currently, there is insufficient data to suggest or refute a relationship between uranium exposure and bone or lymphatic cancer. The most important potential for answering these questions lies with continued follow-up studies of the cohorts of uranium workers because of the range of latency periods between exposure and disease diagnosis.

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(U) This manuscript summarises the risks associated with uranium exposure. Experimental data is available from genetics, tissue culture, and animal and human models. Studies include solubility of different uranium compounds, kinetic properties inside the body, and short- and long-term health effects both from acute and chronic exposures. The potential for uranium entry into the body is highly dependent upon its chemical and physical properties. Inhalation and dermal contact afford the most rapid route of entry, while gastrointestinal absorption is often minimal. The kidneys are efficient at clearing uranium dissolved in the blood, usually within days. Insoluble forms of uranium such as imbedded shrapnel can remain in the body for many years, resulting in persistent elevated levels of uranium in urine. The most important potential for uranium toxicity lies with its chemical properties – not its radiological properties. The most probable health outcomes for uranium toxicity are kidney disease and cancer. Limited data suggests that cumulative pulmonary exposure up to 25 cGy probably does not increase the risk of lung cancer. Nevertheless, there are many gaps in the understanding of the toxicological profile of uranium. Filling these gaps requires monitoring exposed individuals for long periods of time due to the range of latency periods between exposure and health outcome diagnosis.

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uranium, depleted uranium, DU, heavy metal